REMARKS

The claims have been amended in response to the rejection under 35 U.S.C. § 112, paragraph 2, for clarification. In claim 13, it is clarified that the primers target a first nucleotide sequence and that it is the first nucleotide sequence that generates the phenotypic characteristic. In addition, the criterion for prioritizing the extracted gene sequences is set forth explicitly. Support for this amendment is found on page 7, line 22, since alignment of selected gene sequences is based on similarity and identity. This is further explained in the section on alignment tools on pages 14-17, line 13.

The Invention

The invention is directed to a gene discovery method which depends on designing primers that will be useful in targeting and cloning previously unknown genes associated with a desired phenotypic characteristic. Often, the nucleotide sequences associated with a particular phenotypic characteristic will be known in one or more organisms, but the corresponding nucleotide sequences are unknown in an organism of interest. Such phenotypic characteristics would include the activity of the gene product itself, the pattern of expression or the downstream sequelae of such an activity. A multiplicity of databases is available where nucleotide sequences are annotated with regard to the activity of the encoded protein and/or the pattern of expression and/or the natures of the downstream sequelae. Thus, in outline, the method involves starting from a known gene in a particular organism that is associated with a phenotypic characteristic. Since the nucleotide sequence of this gene is known, it can be matched to sequences in commonly available databases such as GenBank, EXProt and IMGT. This matching will result in a set of "extracted" nucleotide sequences that are both similar to the original nucleotide sequence and are annotated to have the phenotypic characteristic. These extracted sequences

will have consensus regions that permit the design of primers. However, where the degrees of alignments are greater, the consensus regions may be different that those surmised from the entire group. Thus, the step of prioritizing the extracted nucleotide sequences to select those with the greatest levels of identity and similarity is useful. Similarly, although not as crucial, perhaps, is the step of filtering out sequences that are common to nucleotide sequences in general to enhance the probability that the primers designed will be focused on the desired nucleotide sequence.

Thus, the ultimate goal is to identify the "first" nucleotide sequence in an organism that is responsible for a phenotypic characteristic for which sequences responsible for this phenotypic characteristic in other organisms are known. The method relies on the availability of annotated databases which match these phenotypic characteristics to known nucleotide sequences.

Responses to the Objections Raised by the Office

Applicants greatly appreciate the apparent withdrawal of the rejections previously made under §§ 101 and 102. Many of the rejections under 35 U.S.C. § 112, second paragraph, previously made, have been withdrawn in light of amendments to the claims. However, substantial rejections remain and the following comments address these issues.

Formal Matters

The present amendment contains amendments to the specification and drawings and Formal Drawings are submitted herewith. It is noted that Figure 7 was not submitted with the original application; Figure 7 is not essential to an understanding of the invention and the specification has been amended to take account of the omission of this figure and the remaining figures are renumbered correspondingly.

The rejection under 35 U.S.C. § 112, paragraph 2, is considered a formal matter as well; claims 13, 34, and 60, the independent claims have been amended to clarify that the primers are designed to target a first nucleotide sequence and it is the nucleotide sequence that results in the relevant phenotypic characteristic. The Examiner correctly states that the primers themselves do not result in a phenotype. Rather, the primers are designed to target a nucleotide sequence that does.

With respect to the objection to claim 16, the intended use for the primers would include cloning the first nucleotide sequence; in addition simply to targeting this sequence, the primers may be used to recover clones thereto. Thus, claim 16 has been clarified to replaced "genetic material" with "said first nucleotide sequence." It is believed this clarifies the issue.

The nature of the objection to claim 18 has not been articulated, and thus applicants are unable to respond.

The Rejections Under 35 U.S.C. § 112, Paragraph 1

One aspect of this rejection is with respect to new matter.

With respect to claims 13 and 60, amendments have been made to clarify that the databases simply annotate their sequences to indicate the phenotypic data. A number of such databases are available, including GenBank, EXProt available on the web at the world wide web address cmbi.kun.nl/exprot/; and IMGT available at imgt.cines.fr:8104/.

Claim 14 has been amended to conform to the text on page 20. The filtering removes from consideration regions which are common both to the desired nucleotide sequences and to nucleotide sequences encoding proteins in general.

With respect to the objection to claim 34, applicants are uncertain as to exactly what the objection is. Original claim 34, which is considered part of the specification, was directed to a system that contained a computer with a communication link between the computer and one or more databases; claim 35 provided for at least one additional computer having the ability to perform the method of claim 1. Thus, it appears that claim 34, as it presently appears, is not new matter - more than one computer was envisioned in the original claims 34 and 35 and a communication link to the databases was present in original claim 34.

Accordingly, the above rejections, based on the assertion that new matter has been added, may be withdrawn.

The remaining rejection, apparently applied to all claims, is based on lack of enablement/written description in consideration of the *Wands* factors. The first criticism is that the nature of phenotypic characteristics is not clearly described. Respectfully, it is believed that "phenotypic characteristic" is a commonly understood term that covers a multiplicity of characteristics too numerous to set forth in any practical way in the specification. As noted above, the characteristic may be as simple as the activity of an encoded protein, the expression pattern of the protein (such as expression in an insect midgut), a known downstream consequence of the activity of the encoded protein or a downstream consequence where the role of the protein is not known (for example, the association of certain oncogenes with the onset of cancer). As such phenotypic characteristics are annotated in publicly available databases, no guidance is required. The nature of the phenotypic characteristic will be dependent entirely on the interest of the practitioner who intends to practice the invention. For example, if the practitioner were interested in the nature of phosphatase genes present in the muscle of domestic cats, the practitioner would extract from databases nucleotide sequences that encode

phosphatases present in muscles of other species where the nature of the genes is known. The choice of the phenotypic characteristic is entirely arbitrary and subject to the discretion and interest of the practitioner; there is no need for the applicants to instruct the practitioner in what he/she should be interested in finding.

The second aspect of this rejection relates to what is said to be the "second step" of claim 13; the description that follows appears to include all steps up to the very final step of designing the primers based on matching portions. The Office goes on to indicate the high degree of guidance provided by the specification. The only negative comment regarding the description and support is that putatively "the primer design described was not practiced following the claimed method."

Applicants do not understand this comment. Applicants fail to see anything inconsistent in Examples 1 and 2 with the sequence of steps recited in the claims. Further, there is no need for the examples to illustrate each and every possible way of carrying out the invention. Further explanation of this basis for rejection might be helpful.

The Office then states that the "portion" referred to is not quantitated precisely. Respectfully, this parameter is well within the judgment of the ordinary skilled artisan and cannot be quantified. One simply looks for regions of the nucleotide sequences that match up. These regions may turn out to be small or large, depending on the particular nucleotide sequences involved. It is submitted that the term "a portion" is sufficiently definite to identify the nature of the regions to be sought. The criteria, of course, are the degree of matching of the identified portions. As to how it is known that the sequence extracted will have the phenotypic characteristic - this is a result of the annotation of the database, as required by the claims.

Similarly, prioritization is an understood concept and is based on the degree of similarity or identity of the sequences - clearly those which align more closely will have higher priority.

Applicants respectfully dispute the assertion that "absent clear and illustrative guidance as to how to particularly perform the above invention, there would be undue experimentation required." Those involved in bioinformatics understand perfectly how to carry out the steps set forth in the claims almost without further explanation.

As to the asserted lack of guidance with regard to integrating various software products, perhaps the best answer to this resides in the statement that follows that "the skill of those in the art of molecular biology is high." However, the appropriate audience for the present claims is not the practitioners of molecular biology, but rather the practitioners of bioinformatics and computer science. A bioinformatics professional would clearly be able to take the approach set forth in the claims in conjunction with publicly available software and databases to carry out the method of the invention. The Office has offered no evidence to show that one of skill in computer software design and bioinformatics would be unable to practice the invention. Accordingly, it is believed that this basis for rejection may be withdrawn.

CONCLUSION

The claims have been amended to clarify the invention and the invention has been described in prose terms in this response. Those with commonly available computer and bioinformatics skills would clearly be able to practice the claimed invention without undue experimentation - the invention lies in the concept of using a known nucleotide sequence associated with a phenotypic characteristic as a search tool in databases annotated for phenotypic characteristics for additional sequences having similar physiological functions and extracting,

prioritizing and optionally filtering these to obtain consensus sequences on which to base primer design. The details of computer software to carry out these functions is now commonplace among computer professionals. Accordingly, it is believed that all pending claims, independent claims 13 and 60, independent claims using other claims for definition, claims 34 and 81, and their dependent claims, claims 14-19, 23, 25-26, 36-41, 45, 47-48, 61-62, 64-66, 70, 72-73 and 82 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 524182000200.

Respectfully submitted,

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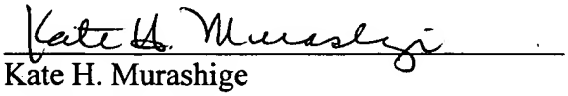
By: 

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